Supplementary Text 2: Bayesian parameter refinement

With the assumptions that parameter priors and data error are normally distributed [1, 2, 3], the task of identifying the posterior parameter values using the Bayesian methodology of *maximum a posteriori* (MAP) is equivalent to solving a weighted minimization problem. The covariance matrix for the prior distribution C_k is taken to have a diagonal structure reflecting parameter uncertainties given in [3]: for parameters k_i which have an informative prior (that is, those given in [3] as well as $r_{\text{in}}^{\text{ApoB}}$), $(C_k)_{ii}$ is the variance of the prior distribution; for parameters which have an uninformative prior (namely, $k_{\text{out}}^{\text{ApoB}}, k_{\text{out,linear}}^{\text{LDL}}, E_{\max}$ and EC50), $(C_k)_{ii} = \infty$. That is, the following prior distribution is assumed:

$$p(k) \propto \exp\left(-\frac{1}{2}(k - k_{\text{prior}})^T C_k^{-1}(k - k_{\text{prior}})\right). \tag{1}$$

Let d_{DG_i} denote the vector of calibration data for each of 3 the dose groups, such that $\text{DG}_i \in \{80\text{mg}, 180\text{mg}, 420\text{mg}\}$. We divide the set of parameters into those that are common across dose groups, k_{comm}, and those that vary between the 3 dose groups k_{DG_i}, where $\text{DG}_i \in \{80\text{mg}, 180\text{mg}, 420\text{mg}\}$. In particular, the latter set consists of the following 3 parameters: $k_{\text{DG}_i} = \{k_{\text{ABCA1}}, r_{\text{in}}^{\text{VLDL}}, r_{\text{in}}^{\text{ApoB}}\}$, while k_{comm} consists of the remaining parameters listed in Table **??**. For each parameter set corresponding to a dose group, $[k_{\text{comm}}; k_{\text{DG}_i}]$, let $G([k_{\text{comm}}; k_{\text{DG}_i}])$ denote the nonlinear mapping from the model parameters to the observation, representing the model simulation of the data. Furthermore, for each dose group DG_i, let $C_{d_{\text{DG}_i}}$ denote the diagonal matrix with the entries representing SEM of the corresponding data points. Hence, for each dose group, the conditional distribution [2] of the data given the model parameters is:

$$f(d_{\text{DG}_i}|[k_{\text{comm}}; k_{\text{DG}_i}]) \propto$$
$$\exp\left(-\frac{1}{2}(G([k_{\text{comm}}; k_{\text{DG}_i}]) - d_{\text{DG}_i})^T C_{d_{\text{DG}_i}}^{-1}(G([k_{\text{comm}}; k_{\text{DG}_i}]) - d_{\text{DG}_i})\right).$$

For each dose group, the posterior distribution $q([k_{\text{comm}}; k_{\text{DG}_i}]|d_{\text{DG}_i})$ is given by the product of terms $f(d_{\text{DG}_i}|[k_{\text{comm}}; k_{\text{DG}_i}])$ and $p(k)$. Hence, to find the MAP solution which minimizes the posterior, the following nonlinear least squares problem is solved: with the objective function for each dose group defined as,

$$\chi^2_{\text{DG}_i}([k_{\text{comm}}; k_{\text{DG}_i}]) \equiv$$
$$(G([k_{\text{comm}}; k_{\text{DG}_i}]) - d_{\text{DG}_i})^T C_{d_{\text{DG}_i}}^{-1}(G([k_{\text{comm}}; k_{\text{DG}_i}]) - d_{\text{DG}_i})$$
$$+([k_{\text{comm}}; k_{\text{DG}_i}] - k_{\text{prior}})^T C_k^{-1}([k_{\text{comm}}; k_{\text{DG}_i}] - k_{\text{prior}}),$$

the MAP solution, k_{MAP}, is the minimizer for the sum over the 3 dose groups:

$$k_{\text{MAP}} \leftarrow \min_{[k_{\text{comm}}; k_{\text{DG}_{80\text{mg}}}; k_{\text{DG}_{180\text{mg}}}; k_{\text{DG}_{420\text{mg}}}]} \sum_{\text{DG}_i=}^{80\text{mg},180\text{mg},420\text{mg}} \chi^2_{\text{DG}_i}([k_{\text{comm}}; k_{\text{DG}_i}]).$$

The above nonlinear minimization problem was solved using genetic algorithm `ga` from the `Matlab`® Global Optimization Toolbox of MathWorks[1]. The hybrid option was selected with the following settings: 100 generations of the genetic algorithm was run with a `PopulationSize`=300, followed by constrained minimization with the setting `MaxFunEvals=20000`, `MaxIter=500`. In all numerical integration of ODEs, the relative and absolute tolerances were set to 10^{-10} and 10^{-12} respectively. The obtained solution k_{MAP} is listed in Table 2.

References

[1] Aster, R., Borchers, B., Thurber, C.: Parameter Estimation and Inverse Problems. Academic Press, Burlington, Massachusetts, USA (2005)

[2] Eydgahi, H., Chen, W.W., Muhlich, J.L., Vitkup, D., Tsitsiklis, J.N., Sorger, P.K.: Properties of cell death models calibrated and compared using Bayesian approaches. Mol. Syst. Biol. **9**, 644 (2013)

[3] Lu, J., Hübner, K., Nanjee, M.N., Brinton, E.A., Mazer, N.A.: An in-silico model of lipoprotein metabolism and kinetics for the evaluation of targets and biomarkers in the reverse cholesterol transport pathway. PLoS Comput. Biol. **10**(3), 1003509 (2014)

[1] http://www.mathworks.com/